REVIEW ARTICLE

Vaccination of adults with asthma and COPD

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Abstract

Vaccines play a major role in preventing potentially life-threatening diseases. More attention is now focused on the adult population, particularly as they age, as a reservoir for vaccine-preventable diseases. Adults with comorbid conditions such as asthma and chronic obstructive pulmonary disease (COPD) are considered to be at higher risk for invasive diseases, many of which are preventable through routine vaccination. This article reviews the pertinent literature for the use of vaccines in the management of adult patients with asthma and COPD.

Vaccines play a major role in preventing potentially life-threatening diseases. In the past 30–40 years, polio has been essentially eliminated, and invasive *Haemophilus influenza* has dramatically declined secondary to childhood vaccination. More attention is now focused on the adult population, particularly as they age, as a reservoir for vaccine-preventable diseases (1, 2). Implementation of guidelines published by the Center for Disease Control (CDC) for the routine vaccination of adults has been effective in reducing the transmission of as well as protection against various illnesses.

As with children, certain populations are at higher risk for vaccine-preventable diseases in adults, e.g., patients with asthma and patients with chronic obstructive pulmonary disease (COPD), both chronic inflammatory lung diseases with significant morbidity and mortality. Viruses play a significant role in the development of asthma, and both viruses and certain bacteria, including *Streptococcus pneumoniae* and *Bordetella pertussis*, play a role in acute exacerbations of both of these disorders (3–8). This article reviews the pertinent literature for the use of vaccines in the management of adult patients with asthma and COPD.

Influenza

The human influenza virus is a single-stranded RNA virus of the family *Orthomyxoviridae* and includes infectious strains A, B, and C. Influenza A and B not only cause seasonal human epidemic disease but also have caused several pandemics. The human influenza virus typically undergoes slight genetic changes each year (antigenic drift) leading to an increased risk of infection because of evasion of host immunity. More abrupt mutations in two surface proteins, hemagglutinin (H) and neuraminidase (N), can lead to influenza epidemics because of creation of a new subtype of influenza virus to which most humans have no resistance (antigenic shift). In 2009, a novel strain of the H1N1 influenza A virus, which evolved in pigs, began to infect humans and is believed to be an example of such mutations (9).

Each year, the influenza vaccine is an injectable trivalent, inactivated viral vaccine (TIV) composed of seasonal H3N2, H1N1, and Influenza B. The World Health Organization's (WHO) Global Influenza Surveillance Network, in conjunction with the CDC, determines the strains that pose the greatest chance to cause human illness and is based upon data collected from 122 national influenza centers in 94 countries. The WHO recommendations are published for the northern hemisphere in February and for the southern hemisphere in September (10). Since 2003, a live-attenuated vaccine (LAIV) has been available, also containing the three WHO recommended influenza strains.

Seasonal influenza has a significant impact on the population with more than 200 000 hospitalizations and 36 000

deaths annually in the United States (11, 12). Indirect health care costs are estimated to be $4.6 billion annually, with 111 million lost work days (13). In subjects with asthma, influenza has been linked with the development of disease, and in both asthma and COPD influenza can contribute to acute exacerbations (14). Influenza infection leads to an increased risk of hospitalization in COPD (15). Viruses, including influenza, cause acute exacerbations of asthma in as many as half of adult subjects presenting to emergency rooms (5). Eighty percent of children aged 9–11 who had an asthma exacerbation and subsequent declines in peak flow had detectable virus, including influenza, in nasal aspirates (16). In a study by Miller et al., (17) children with asthma were more likely to have outpatient physician visits and hospitalization owing to influenza compared to healthy controls.

Influenza plays a significant role in exacerbations of both asthma and COPD, but there are concerns about the effectiveness of influenza vaccination in these populations. Several observational studies show a reduction in the number of hospitalizations, incidence of pneumonia, risk of death, and number of acute exacerbations in COPD patients who received the influenza vaccine; however, to the contrary, a 2003 case–control study of adults with COPD and asthma found no reduction in the number of severe or fatal complications after influenza vaccination (18–22). A 2006 Cochrane review found evidence of a decreased number of acute COPD exacerbations after vaccination, but the studies included were too small to determine any effect on mortality (21). In asthma, several studies demonstrate a reduction in the number of exacerbations following vaccination, but others have not (23–26). An increased risk of exacerbation following vaccination has been a postulated side-effect in subjects with asthma and COPD. Several studies including a 2001 study of more than 2000 children and adults and a 2008 Cochrane review found no significant increase in exacerbations in the 2 weeks following vaccination (23, 27, 28).

Data comparing the effectiveness of the inactive *vs* live-attenuated vaccine are still conflicting. A 2006 study of children and adolescents with asthma found a greater decrease in community-acquired influenza after live-attenuated vaccination than those who received the inactivated vaccine with no significant change in asthma symptom scores, peak flow, or number of exacerbations (29). Subjects receiving the live-attenuated vaccine did have a higher incidence of rhinorrhea. In adults, a study during the 2007–2008 influenza season found that the inactivated vaccine was more efficacious in preventing influenza A than the live-attenuated vaccine (30).

Inhaled (ICS) as well as systemic corticosteroids are common medications used to treat asthma and COPD. Corticosteroids can impact the immune system by decreasing both T and B lymphocyte numbers and immunoglobulin levels (31–34). This effect is dose dependent and can be prolonged with repeated use of these medications. ICS use does not decrease responsiveness to influenza A immunization; however, high-dose ICS use does decrease the responsiveness to influenza B (35). Although there are no controlled trials analyzing the effect of daily systemic corticosteroid use on the effectiveness of the influenza vaccine, a prospective study by Fairchok et al. (36) showed that high-dose oral corticosteroid bursts (2 mg/kg per day) did not decrease immunogenicity to influenza vaccination. Similar results were found by Park et al. (37) in a cohort of children treated with systemic corticosteroids who were vaccinated during an acute asthma exacerbation.

Concern about the incidence of Guillain–Barre syndrome and influenza vaccination has also been raised. Guillain–Barre syndrome is an acute inflammatory demyelinating polyneuropathy, characterized by ascending paralysis that can lead to respiratory compromise, and occurs in 1–2 cases per 100 000 adults (38). Multiple infectious agents, including influenza, have been linked to development of this syndrome (39, 40). In 1978, there was an increased incidence of Guillain–Barre syndrome in swine-H1N1 influenza vaccines, leading to discontinuation of the vaccine program (41). There is a postulated vaccine-attributable risk of developing Guillain–Barre after influenza vaccination, but several large cohort studies have shown no increased incidence of this syndrome after vaccination and may in fact be protective (40, 42–46). Data from the 2009–2010 season show no increased risk of adverse events, including Guillain–Barre syndrome, after swine-H1N1 vaccination (47).

Although there is some debate, the Advisory Committee on Immunization Practices (ACIP) and the CDC (http://www.cdc.gov/vaccines/recs/acip/) recommend that all patients with asthma and/or COPD receive the influenza vaccination on an annual basis. There does not appear to be any significant adverse reactions nor increase in acute asthma or COPD exacerbations after receiving either the live-attenuated or inactivated influenza vaccines. Contraindications to the live-attenuated vaccine include pregnancy and immunodeficiency states including HIV infection, regardless of CD4 count. Pregnant women can receive the inactivated influenza vaccine at any time during pregnancy. Egg-allergic subjects or those with anaphylaxis to other components of the vaccine should not receive either influenza vaccine without consulting their physician. Several studies show that it is safe to administer the influenza vaccine without prior testing in egg-allergic subjects, especially if the ovalbumin content is < 1 μg per 0.5 ml dose (48, 49). As there are no controlled studies analyzing the potential risk of live-attenuated influenza vaccination, patients with unstable asthma should receive the inactivated vaccine.

Streptococcus pneumoniae

Streptococcus pneumoniae (pneumococcus) is a Gram-positive coccus that causes a variety of diseases in both children and adults, including meningitis, sepsis, and pneumonia. Pneumococcus colonization occurs more frequently in the airways of patients with COPD when compared to healthy controls (50). When present, it is associated with a higher risk of COPD exacerbation (51). Patients with asthma can also be colonized with pneumococcus and when present are at more risk of exacerbation and invasive pneumococcal disease (52, 53). In children, *S. pneumoniae* colonization of the upper airway is associated with an increased risk of wheezing and asthma (54). Subjects with asthma and other atopic disorders are at

higher risk of invasive pneumococcal disease when compared to those without these conditions (7, 53, 55).

The adult pneumococcal vaccine is a 23-valent polysaccharide vaccine (PPSV23) that is approved for prevention of invasive disease in adults. Serotypes include 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F that represent the most common types associated with invasive disease in the United States (56). Although PPSV23 is the only vaccine approved for use in adults, a study published by Dransfield et al. (57) found that the 7-valent conjugated vaccine induces a better immune response than the 23-valent polysaccharide vaccine, indicating that an adult conjugated vaccine may be more effective than PPSV23.

Studies of the effectiveness of the pneumococcal vaccine in patients with COPD are mixed. Several retrospective studies show a reduction in incidence of community-acquired pneumonia, hospitalizations, as well as prevention of invasive disease (58–60). A 2008 Cochrane review of adults found a reduction in invasive pulmonary disease after pneumococcal vaccination but no reduction in all-cause pneumonia or mortality. Results in subjects with chronic illnesses were unclear (61). A 2006 Cochrane review of four studies and a 2009 non-Cochrane meta-analysis of 22 trials found no reduction in the incidence of pneumonia or mortality, even in groups for whom the vaccine is recommended (62, 63). Two studies in Japan did show a reduction in bacterial infections and acute exacerbations of COPD in subjects receiving both influenza and pneumococcal vaccines when compared to either alone (64, 65).

There are limited data available for the role of PPSV23 in asthma. A 2002 Cochrane review found only one study of PPSV23 and asthma which met their entry requirement for review. This study found a reduction in the number of acute exacerbations following PPSV23 vaccination, however, a study by Lee et al. found no significant difference in the relative risk of hospitalization owing to pneumococcal pneumonia after PPSV23 in patients with asthma compared to controls (59, 66).

There are no controlled trials analyzing the effect of ICS on response to pneumococcal vaccination. In regard to systemic corticosteroids, Steentoft et al. (67) found no differences in vaccine response between COPD subjects on systemic corticosteroids (prednisolone 37.5 mg tapered over 4 weeks) *vs* COPD subjects off systemic therapy. Similar results were found by de Roux et al. (68) in COPD subjects taking greater than prednisolone 10 mg per day or an equivalent dose of another corticosteroid. A study by Lahood et al. (69) showed that chronic, daily corticosteroid use in adults with asthma (prednisone 10–35 mg/day) does not affect serum antibody levels to pneumococcus.

The overall benefits of vaccination against pneumococcus remain controversial. Despite this, both ACIP and CDC recommend vaccination for all adults with asthma, COPD, and cigarette smokers. It is recommended for all adults over the age of 65 and any patient 2 years or older at high risk for invasive disease, including smokers and patients with chronic lung disease. Revaccination is recommended for patients at high risk of invasive disease and should be given no sooner than 5 years from the previous vaccination, owing to potential increased risk of adverse effects if given sooner (56). Patients 65 or older should only be revaccinated if the previous dose occurred when they were less than 65. Contraindications include a previous history of anaphylaxis to vaccine components and pregnancy, although women at risk of invasive pneumococcal disease should be vaccinated prior to pregnancy.

Pertussis

Bordetella pertussis, a Gram-negative coccobacillus, causes the highly communicable disease pertussis, or 'whooping cough', characterized by three phases of cough: catarrhal, paroxysmal, and convalescent. Subjects are at risk of complications including pneumonia, encephalopathy, seizure, and pulmonary hypertension. There are between 5000 and 7000 cases of pertussis in the United States each year. Epidemics of the disease typically occur every 3–5 years, with the latest reported in 2005 (70). The incidence of pertussis has increased since the 1980s, reaching a peak in 2007 with 10 454 cases. Three to twelve percent of adults with pertussis require hospitalization, 4% develop rib fractures owing to coughing, and 5% of subjects develop pneumonia. Adults are believed to be an important reservoir for both children and other adults owing to waning immunity (71–74).

Infection with *B. pertussis* can lead to worsening of asthma symptoms. A cohort of Canadian adults with asthma had longer periods of cough, more nighttime symptoms, and increased rescue medication use during their illness (8). Thirty of 103 patients in a study analyzing the frequency of colonization of the respiratory tract of adults with stable asthma had evidence of *B. pertussis*, and these patients had lower FEV1/FVC and more symptoms than asthmatics who were culture negative for pertussis (75). Serologic evidence of *B. pertussis* has been also documented in acute exacerbations of chronic bronchitis (76).

Tdap (Tetanus, diphtheria, and acellular pertussis) is the current vaccine approved by the ACIP in adults for prevention of pertussis. The vaccine contains a reduced portion of diphtheria and detoxified pertussis toxin compared to the pediatric diphtheria, tetanus, and acellular pertussis vaccine (DTaP). Studies show that the immunity induced by Tdap is equivalent to that of DTaP (77). Analysis of the adult vaccine program demonstrates that a one-time vaccination with Tdap would reduce the incidence of pertussis by 44% over a 10-year period and could possibly reduce the transmission to children (71).

Although there are no human trials on the effectiveness of pertussis vaccination in asthmatics, a study in the murine model shows that the acellular pertussis vaccine can reduce the severity of airway pathology and hyperreactivity to methacholine (78). Another murine study by Ennis et al. (79) shows that vaccination with whole-cell pertussis prevents allergic asthma exacerbations. These studies suggest a role for vaccination against *B. pertussis* in patients with asthma.

There also are no studies on the effects of vaccination against pertussis in patients with COPD; however, pertussis has been shown to play a role in acute exacerbations; thus vaccination may also be beneficial in this group (75).

Both CDC and ACIP recommend Tdap in all adults aged 19–64, including those with asthma and COPD. Although studies in these populations are limited, the vaccine is safe and may confer significant benefit. It is recommended as a single dose in adults 19–64 years of age, if the previous dose of tetanus (Td) was at least 10 years prior. It can be given in a shorter interval if a subject is considered at high risk for exposure to *B. pertussis*. If an adult has not been previously vaccinated against tetanus, diphtheria, or pertussis, they should complete a three-part series containing both tetanus and diphtheria vaccines. The CDC recommends the first vaccine be Tdap, followed by Td at least 4 weeks later, and a third Td six to twelve months after the second dose. The only contraindication to use of Tdap is a previous history of anaphylaxis or seizure after vaccination. In pregnant women, the ACIP recommends that Td be given during pregnancy rather than Tdap owing to a lack of safety data in this population. It is recommended, however, that women of child-bearing age receive Tdap prior to becoming pregnant or during the postpartum period.

Herpes zoster

The varicella zoster virus (VZV) is one of eight herpes viruses that infect humans. It is the cause of chicken pox, after which it becomes dormant in the dorsal root ganglia. VZV is typically a self-limited disease but may be complicated by superinfection of skin lesions with *Staphylococcus aureus*. It is also associated with VZV-pneumonia and CNS diseases, including encephalitis, Reye's syndrome, and Guillain-Barre syndrome. Approximately 20% of patients will have reactivation of the virus leading to herpes zoster, or 'shingles', a unilateral dermatomal distributed vesicular rash, which can be complicated by postherpetic neuralgia, blindness, hearing deficits, or facial paralysis.

Aging patients, owing to normal decline in cell-mediated immunity, as well as those who are immunosuppressed owing to other causes, are particularly at risk for varicella reactivation. A live-attenuated vaccine for the prevention of herpes zoster (Zostavax®; Merck and Co, Inc., Whitehouse Station, NJ, USA) was approved in 2006. Vaccine studies carried out prior to approval show a decrease in the incidence of herpes zoster in healthy adults aged 60 or older by 51.3% and postherpetic neuralgia by 66.5% (80). Although there are no controlled studies analyzing the risk of development of herpes zoster in patients with asthma or COPD, use of high-dose ICS or systemic corticosteroids may lead to partial immune suppression and an increased risk of zoster reactivation, especially in aging adults. There are no data on the possible effects of ICS or systemic corticosteroids on the effectiveness of Zostavax®, although studies are currently underway.

Zostavax® is approved as a onetime dose for prevention of herpes zoster in patients aged 60 and older as well as those with chronic medical conditions including chronic lung diseases. It is also recommended in subjects with a previous history of zoster reactivation owing to risk of a second reactivation. It should also been given to adults with no known history of chicken pox and may provide some protection from future varicella infection. Zostavax is not considered

Table 1 Recommended vaccination schedule for adult patients with asthma and COPD*

	Manufacturer (USA)	Initial vaccination	Revaccination	Contraindications
Influenza	*Inactivated (TIV)*: FluZone® (Sanofi Pasteur) FLUVIRIN® (Novartis) FLUARIX® (GlaxoSmithKline) FluLaval™ (GlaxoSmithKline) AFLURIA® (Merck) *LAIV*: FluMist® (MedImmune)	Once yearly (any age)	Yearly	*TIV/LAIV*: Egg allergy, anaphylaxis to vaccine components *LAIV*: Immune deficiency states (including HIV), pregnancy, unstable asthma
Pneumococcus (PPSV23)	Pneumovax® (Merck)	Once	*18–65*: Revaccination 5 years after initial vaccination *≥65*: One time vaccination, unless first dose was given at age <65 and 5 years have passed	Anaphylaxis to vaccine components, pregnancy
Pertussis (TdaP)	Boostrix® (GlaxoSmithKline)	Once between age 19–64, replaces one dose of Td	None	Anaphylaxis to vaccine components, seizures after previous vaccination
Herpes zoster	Zostavax® (Merck)	Age 60 or older, regardless of previous Zoster outbreak	None	Immune deficiency states (including HIV), pregnancy

*Adapted from Centers for Disease Control (CDC) vaccine guidelines and recommendations found at http://cdc.gov/vaccines/recs/schedules/adult-schedule.htm. Information regarding vaccine manufacturers available at http://www.immunize.org/resources/manufact_vax.asp.
CPOD, chronic obstructive pulmonary disease; TIV, trivalent inactivated viral vaccine; LAIV; live-attenuated vaccine.

a treatment for concurrent shingles. Contraindications to Zostavax® include patients with immune suppression, including patients on more than prednisone 20 mg/day, or its equivalent. It is also contraindicated in pregnant women and subjects with HIV infection regardless of CD4 count.

Conclusions

Viruses and several bacteria play a role in acute exacerbations of both asthma and COPD, leading to significant morbidity as well as increased health costs. Early recognition and prevention of these pathogens continues to be an important goal of all health care professionals who care for these populations. Although vaccines have been shown to be highly effective in preventing a variety of serious illnesses, additional work is needed to clearly define their role in subjects with asthma and COPD. As recommend by the CDC and ACIP, physicians and other health care professionals should continue to vaccinate subjects with asthma and COPD against influenza, pneumococcus, pertussis, and herpes zoster. A summary of available vaccines in the United States and dosing schedules is given in Table 1. As worldwide vaccine recommendations vary, physicians and other health care professionals should check for regional vaccination schedules and approved vaccines with local health care authorities.

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